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RESECTION OF LUNG CANCER INVADING THE DIAPHRAGM

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Non–small cell lung cancer (NSCLC) invading the diaphragm is a rare stage III disease with a poor prognosis. In 1997, Weksler and associates[1] reported the only study concerning its surgical management, observing 8 cases among 4688 patients undergoing exploration for resection of NSCLC. In 1998, Inoue and colleagues[2] reported 5 other cases and suggested that such NSCLC invading the diaphragm may be a candidate of the T4 TNM subgroup. Doyle and Aisner[3] attributed such a bad prognosis to the extensive venous and lymphatic drainage from the diaphragm that almost invariably results in disease outside the scope of surgery, further explaining that "once cancer cells have crossed both the visceral and parietal layers of pleura into diaphragmatic muscle, there is almost always invasion of the liver or metastases to the retroperitoneal lymph nodes or both." For this entity to be further evaluated and explained, the examination of a larger number of cases was mandatory. This was the purpose of this retrospective multicentric study.

Patients and methods. We retrospectively reviewed the cases of 68 patients who had exploratory thoracotomy for resection of NSCLC invading the diaphragm. These patients were operated on in 17 different centers from February 1976 to February 1998. There were 56 men and 12 women. The mean age was 61 years (range, 35-85 years); 22 tumors were on the left, and 46 were on the right. All patients were free of clinical metastatic disease, as determined by chest computed tomography (CT), brain CT, abdominal CT, or ultrasonography. Mediastinoscopy was not routinely performed. Induction chemotherapy was performed in only one case. Postoperative adjuvant radiation therapy (n = 29), postoperative radiation and chemotherapy (n = 9), and chemotherapy alone (n = 4) had no influence on survival. We recorded surgical procedures, pathologic findings, N status (as reviewed in 1997[4]), survival, and long-term results, as well as the cause of death. The Kaplan-Meier method was used to estimate survival.

Results. During exploratory thoracotomy, 3 patients were deemed to have unresectable disease, and 6 patients underwent an incomplete resection. A complete resection of macroscopic disease was performed in 59 patients (lobectomy, n = 28; bilobectomy, n = 11; and pneumonectomy, n = 20). The diaphragm was resected en bloc with the tumor in all cases (primary closure, n = 55; reconstruction with a prosthesis, n = 4). The mediastinal lymph node dissection was complete in 39 patients, incomplete in 13 patients (limited to adjacent mediastinal lymph nodes), and not performed at all in 7 patients (pN status in Table I). There were 35 squamous cell carcinomas, 16 adenocarcinomas, 1 adenosquamous carcinoma, 3 large cell carcinomas, 1 undifferentiated neuroendocrine carcinoma, and 1 sarcomatoid carcinoma; histologic pathology was not available in 2 patients. The tumor was adherent to the diaphragm without histologic invasion in 13 patients, and it pathologically invaded the diaphragm in 41 patients (pleural serosa, n = 6; muscle, n = 32; and peritoneum, n = 4). Such data were not available in 4 patients. pN status between groups with or without histologic diaphragm invasion was not significantly different.

There were 3 postoperative deaths (sepsis, n = 1; pneumopathy, n = 2) and 10 postoperative complications (pleuroparietal sepsis, n = 5; fistula, n = 1; pneumopathy, n = 1; prolonged air leak, n = 1; respiratory failure, n = 1; and intestinal obstruction, n = 1). There was no survival beyond 2 years in case of unresected or incompletely resected disease. There was no survival beyond 5 years when mediastinal lymph node dissection was not performed, and there was only one survival at 5 years when mediastinal lymph node dissection was incomplete. The overall 5-year survival was 39% (confidence interval, 30%-48%) in case of complete mediastinal lymph node dissection. Prognosis was not influenced by the degree of pathologic invasion of the diaphragm. Prognosis appeared as bad in N0 cases as in N1 and N2 cases. N+ involvement proved to be very frequent (67%; N1 = 23% and N2 = 44%; Table I). Causes of death (n = 35) are summarized in Table II. Twenty-four patients were still alive, but only 16 (67%) were free of disease.

Discussion. The poor prognosis of this entity was obvious in this series. The attribution by Doyle and Aisner[3] of such a

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Table I. *pN status of completely resected cancers*

	MLND	*N0*	*N1*	*N2 (1)*	*N2 (2)*
Complete	39	13	9	6	11
Incomplete	13	7	4	1	1
Not performed	7	5	2		
Total	59	25	15	7	12

MLND, Mediastinal lymph node dissection; *N2 (1),* 1 anatomic level involved; *N2 (2),* 2 or more anatomic levels involved.[4,5]

Table II. *Causes of deaths (n = 35) in cases of completely resected cancer (n = 59)*

Causes of death	*N0*	*N1*	*N2*	*Total*
Postoperative		2	1	3
Metastases	6	4	8	18
Metastases + local recurrence	3			3
Local recurrence alone	4	1		5
Other cancer	1	1		2
Cancer unrelated	2	1	1	4
Total	16	9	10	35

bad prognosis to the extensive venous and lymphatic drainage from the diaphragm is well demonstrated by this review, revealing the high frequency of lymph node involvement and deaths caused by systemic metastases. The lymphatic involvement mainly spread upward along the anatomic visceral lymphatic pathways of the mediastinum, as shown by the high frequency of N2 disease revealed by mediastinal lymph node dissection and further characterized by a high frequency of involvement of 2 or more anatomic mediastinal levels (65%). The current frequency of such involvement appeared to be only 39% in a population with resected N2 lung cancer.[5] The lymphatic drainage of the diaphragm probably constitutes a pathway for the tumor cells to join the blood circulation through the mediastinum, and this may explain the poor prognosis we observed even in cases of N0 and N1 disease; the 5 cases that prompted Inoue and colleagues[2] to suggest labeling the diaphragm invasion as T4 were also N0 and N1. To conclude, this review confirms that diaphragm invasion is an advanced stage and therefore is a potential indication for neoadjuvant chemotherapy, as suggested by Weksler and associates.[1] Because diaphragm invasion is clinically difficult to assess,[1] we suggest performing video-assisted thoracoscopy for pretreatment T staging to complement mediastinoscopy in cases of cancer with close contact with the diaphragm. On the other hand, this entity may benefit from adjuvant chemotherapy if discovered after surgery.

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